

Reading difficulties in Duchenne muscle dystrophy patients

*Basis of verbal working memory
in cerebellar circuits*

Ina Blandhol



Thesis submitted for the
Professional Program in Clinical Psychology

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Abstract

Author: Ina Blandhol

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Advisor: Nils Inge Landrø

Duchenne Muscle Dystrophy (DMD) is an X-linked genetically inherited disorder, leading to profound muscle weakness and specific cognitive deficits hampering reading capacity and general academic functioning. Improving fundamentals for assessing the DMD children in more specific ways will be crucial for understanding and addressing their special needs for educational support and psychological scaffolding. This work will compare the DMD readers to groups with developmental dyslexia and cerebellar lesion patients showing a wide range of working memory, and language deficits affecting their reading process. The DMD group has been described with specific verbal working memory deficits, specifically pointing towards the inability to perceive sequences of information, a core basis for fluent reading. In addition, difficulties on procedural, attentional and phonological level adds to the risk of dyslexia in DMD. Working memory deficits in DMD can be regarded as a consequence of cerebellar dysfunction. Verbal working memory and sequencing deficits are also found in patients with cerebellar lesions and actualized in reading by the cerebellar hypothesis of dyslexia. A link between DMD dystrophin deficiency, expressed in cerebral and cerebellar tissues, and cognitive impairment in the DMD group is suggested. Placing the cerebellum as a central part in a cerebro-cerebellar signal pathway, and reviewing findings of cerebellar dysfunction in the DMD group, working memory processes and phonological processing, and sequenced memory processes specifically, are plausibly connected to cerebellar function. Using the working memory model presented by Baddeley (2011), the working memory concepts are combined and discussed within current findings from neural imaging and lesion studies, animal models, genetic mapping studies, tissue analyses and neuropsychological assessment methods. The understanding of reading problems in DMD will be drawn from molecular genetics to assessment of practical reading skills, discussing whether these problems could be a result of cerebellar dystrophin deficiency.

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INTRODUCTION

Duchenne Muscle Dystrophy (DMD) is an X-linked genetically inherited disorder mainly affecting boys, even though there are reported female manifesting carriers. The disorder is characterized by dysfunctional coding for the protein dystrophin in multiple tissues throughout the body, including the brain and central nerve system (CNS). Absence of dystrophin in skeletal musculature leads to progressive muscle weakness and profound motor decline. Dystrophin deficiency expressed in cerebral and cerebellar tissues are thought to be responsible for the cognitive impairment in this group (Cyrulnik & Hinton 2008). Drawing lines between expression of genetic profiles and dysfunction in brain tissues, developmental issues are actualized, which in turn calls for comparison to groups with neurodevelopmental disorders and premature babies.

In addition to a lowered level of general abilities DMD patients are generally showing verbal working memory deficits and delayed language development strongly affecting reading abilities and general academic functioning. Reading is a core skill in modern literate society, and reading difficulties have a wide impact on personal performance and self esteem. Improving fundamentals for assessing the DMD children in more specific ways will be crucial for understanding and addressing their special needs for educational support and psychological scaffolding. This work will compare the DMD readers to groups with developmental dyslexia and cerebellar lesion patients showing a wide range of working memory and language deficits affecting the reading process.

Reading problems and verbal working memory deficits presenting in DMD can be regarded as consequences of cerebellar dysfunction. Sequencing deficits may be the core difficulty in the verbal working memory deficits shown, underlying the risk of reading disorders in this group. A cerebro-cerebellar signal path is placing the cerebellum as a central part in the phonological loop, general verbal processing, general working memory, and sequenced memory processes specifically. Suggesting that the specific cognitive deficits presented in DMD has its origin in the cerebellar dysfunction, will evidence from multifocal research support this hypothesis?

The DMD group has been described with specific verbal working memory deficits, specifically pointing towards the inability to perceive sequences of information, a core basis

for fluent reading. Verbal working memory and sequencing deficits are also found in patients with cerebellar lesions and actualized in reading by the cerebellar hypothesis of dyslexia. Can the reading difficulties in DMD be explained by sequencing deficits in verbal working memory as a consequence of dystrophin deficiency in cerebellar purkinje cells?

In a multidisciplinary perspective, the present study search to explore these questions. The understanding of reading problems in DMD will be drawn from gene expression to practical reading skills, broadening the perspectives on core cognitive functioning in this group.

Clinical picture Duchenne muscle dystrophy

Dystrophinopathies are the most common among childhood muscular dystrophies, affecting 1 in 3500-5000 male births (Jeppesen et.al. 2003, Wicksell et.al. 2004). Mutations in the DMD gene are responsible for dysfunctional dystrophin coding in different cell tissues, leading to the development of either the milder Becker muscular dystrophy or the more severe Duchenne muscular dystrophy (Koenig 1989, Tuffery-Giraud et.al. 2008). The incident of Becker and Duchenne muscle dystrophies is about 1/3 BMD to 2/3 DMD (Tuffery-Giraud et.al. 2008).

While most disorders have a cluster of symptoms defining the disorder, having a known genetic etiology, DMD is in the opposite position. Even though there is a significant genetic variation within the DMD group, definitive patterns of physiological and cognitive dysfunction are described.

Physical and cognitive characteristics.

The DMD phenotypical picture is characterized by wide clinical heterogeneity. Neither mutation class nor protein expression can solely distinguish phenotype or characterize progression. There are three widely used diagnostic classes (United Dystrophinopathy Project Consortium) based on age at loss of ambulation: DMD (loss of ambulation at less than age 12); IMD (intermediate muscular dystrophy) (loss of ambulation between ages 12 and 15); and BMD (loss of ambulation at greater than age 15) (Flanigan et.al.2009, Desguerre et.al.2009). These classes do not include descriptions of cognitive function.

Early motor deficits and general motor developmental delay will often appear as first signs, however in some cases language delay may be the earliest sign of DMD (Cyrulnik et.al. 2007). When DMD children (n=130) was compared to their unaffected siblings (n=59), the

DMD children tend to be rated as delayed in most motor and language milestones. They were delayed speaking their first word and constructing sentences, as well as sitting, crawling, standing and walking, but not delayed in controlling bladder and bowel compared to children at the same age. Early developmental delays were found to be associated with significant impairments in later cognitive functioning (Cyrulnik et.al. 2007), indicating that early diagnosis will be important to comprehend the child's vulnerability at an early stage.

DMD children are also at risk for general social functioning problems. A group of preschool children with DMD (n=20) showed delay in adaptive functioning, including communication, daily living, socialization, and motor skills compared to their unaffected siblings (Cyrulnik et.al. 2008). Donders & Taneja (2009) concluded with DMD boys (n=22) as having more difficulties with social interaction, initiation and adaptation than their siblings (n=18), reported by their parents with the Child Behavior Checklist (CBCL) and Behavior Rating Inventory of Executive Function (BRIEF). Other neuropsychiatric disorders more common in the DMD group are autism spectrum, attention deficits, hyperactivity (ADHD), and obsessive-compulsive disorders (Hendriksen & Vles 2008).

The severe and progressive loss of muscle strength is a typical sign of DMD in most patients. Loss of respiratory muscle strength, ineffective cough and decreased ventilation, leads to pneumonia, atelectasis and respiratory insufficiency during sleep and while awake. A majority will in addition develop cardiomyopathy, both conditions contributing to a premature death. (ATS Consensus statement 2004). More efficient methods of diagnosis and better awareness of possible respiratory interventions and care, has prolonged the life of Duchenne patients into adulthood (Jeppesen et.al. 2003). Early medication with corticosteroids will delay muscular destruction, delay age of loss of independent walking and prolong the life expectancy to about 25 years for 53% of the affected boys. Corticosteroid treatment can even improve heart function and delay ventricular dysfunction (Markham et.al. 2008). The latest research on DMD management also focuses on genetic splice-correction therapy (Wood et.al. 2010).

Diagnosing DMD

Being an X-linked genetically inherited disorder, mainly boys are affected (Figure 1). However, female manifesting carriers are common, some presenting with adult muscle weakness, others with cognitive delay or learning difficulties.

Diagnosis is based upon three common markers. Firstly a family history of DMD or suspicion of any abnormal muscle function, secondly a delayed development of walking (not walking ≥ 16 -18 months) and thirdly biochemical markers as unexplained increase in transaminases. Either of these would indicate the need for a detailed creatine kinase (CK) screening. Increased levels of CK can be a marker for DMD, but in order to confirm the diagnosis a muscle biopsy confirming dystrophy deficiency and/or a genetic mapping and mutations found in the DMD gene will be carried out. In those cases where genetic deletions or duplications are not found, a thorough genetic sequencing process will in most cases detect smaller point mutations. (Bushby et.al. 2010).

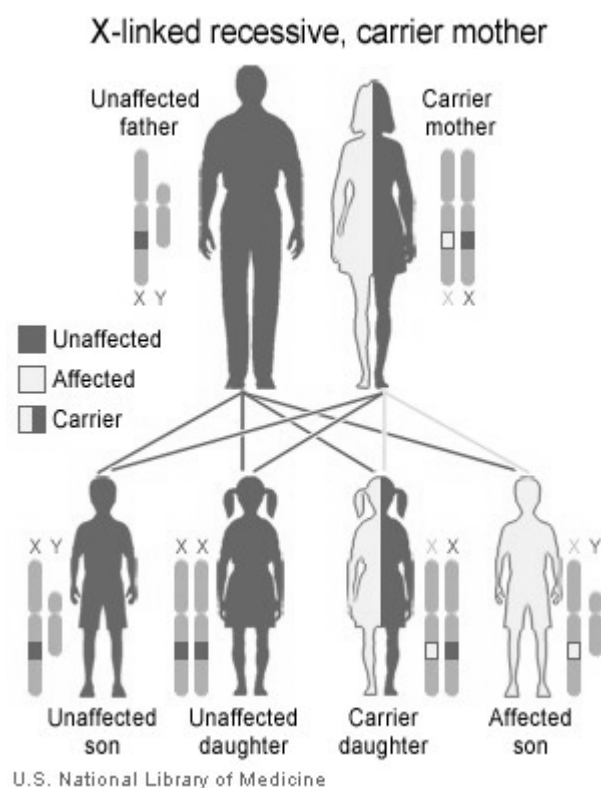


Figure 1 – Duchenne muscle dystrophy - an X-linked disease

The diagnostic process of DMD has lately undergone great changes, from muscle biopsy examination to precise genetic analysis. Muscle biopsy samples have been examined histologically for an abnormal quantity or abnormal molecular weight dystrophin protein, confirming dystrophinopathies and for a diagnostic conclusion differentiating BMD/DMD. The first clinically available genetic testing used multiplex polymerase chain reaction (PCR) and Southern blotting to identify large-scale deletions. Small scale deletions and minor mutations are detected with newer methods of analysis (Flanigan et.al.2009). With the latest

methods of genetic mapping, mutations are detected in more than 95% of patients with a clinical diagnosis of DMD. Muscle biopsy is still used for definitive diagnosis (Cunniff et.al.2009), but the level of creatine kinestase is widely used as an first indicator of further examination and an easily used, reliable, low cost method of diagnosis.

Diagnosing DMD is reported with a delay from the Primary health care system, missing early signs and symptoms. A study of an American DMD population concludes with a mean delay of 2.5 years from DMD symptoms to diagnosis, mean age for diagnosis at 4.9 years (n=156). (Ciafaloni et.al. 2009). Boys presenting with cognitive developmental delay only are at extra risk of having a late diagnosis (Essex et.al.2001). It will be crucial for the child to be diagnosed and tested for cognitive functioning in order to address the special needs and support in the delayed development.

DMD dystrophin deficiency

In dystrophinopathies the deficiency of dystrophin in various forms is causing dysfunction in tissues around the body. Dystrophin is a large 427-kDa cytoskeleton-associated membrane-bound protein; a major component of multiprotein complexes (dystrophin-associated glycoprotein complex, DGC) located at the plasma membrane in both muscle and nonmuscle tissues. DGC provides a scaffold for proteins involved in membrane stabilization and transmembrane signaling in a variety of tissues and cell types, including the postsynaptic membrane of neurons in CNS (Haenggi & Fritchey 2006). Dystrophin is in addition to being involved in the clustering of several membrane receptors and ion channels a modulator of cellular signal integration and synaptic plasticity. Dystrophin plays a direct role in promoting the maturation of the synapses, promoting the density and capacity of sodium channels (Banks et.al. 2009, Perronnet & Vaillend 2010).

The genetics of DMD/BMD

The DMD gene is one of the largest in the human genome, localized to the Xp21. The gene has 79 exons encoding a 14kb mRNA transcript. The corresponding 427-kDa protein is called dystrophin or Dp427, and is expressed in skeletal and cardiac muscles, as well as in the CNS.

Full length dystrophin is derived from three independent promoters M, C and P, regulating the expression of the full length protein in muscles (Dp427-M), forebrain (Dp427-C) and cerebellar Purkinje cells (Dp427-P) respectively (Perronnet & Vaillend 2010). The

short dystrophin isoforms expressions Dp71, Dp116, Dp140 and Dp260 are regulated by four other internal promoters (Figure 2). Depending on the location of the mutation, different isoforms are compromised and not expressed correctly.

The complexity of the DMD gene error expression results in multiple genotypes including a variety of location and genetic coding errors. Any changes and combinations of errors in the normal splicing process, including small mutations of nonsense, mis-sense and small insertion-deletions, nucleotide substitutions, will result in a specific genotype. The most common mutations in the DMD gene are the large intragenic deletions (Muntoni et.al. 2003, Cunniff et.al. 2010, Juan-Mateu et.al. 2010). A deletion is when parts of the gene are missing; building an incomplete protein product not recognized as functional dystrophin. Duplications are rarer, repeating the information several times, giving sometimes a partly functional protein. Both mutations result in a premature translation termination leading to an absence of dystrophin. (Muntoni et.al.2003).

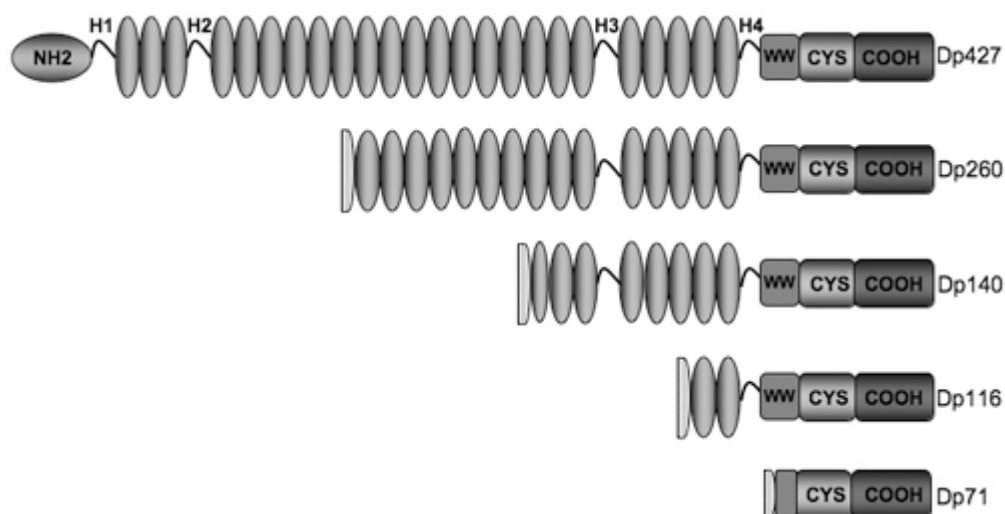


Figure 2 - Dystrophin in the brain (Action Duchenne 2011).

Several genotype-phenotype hypotheses are made to predict severity of motor and cognitive function. Analysis of the DMD gene suggests that at least the severity of motor function is depending on reading frame disruption and premature termination of protein synthesis. Depending on whether the genetic reading frame is intact or lost the mutations in the DMD gene leads in most cases to either the milder Becker muscular dystrophy or the severe Duchenne muscular dystrophy (Koenig 1989, Tuffery-Giraud et.al. 2008). Most mutations in the DMD gene are out-of-frame, causing complete loss of dystrophin (Perronnet & Vaillend 2010). In the milder BMD some internally truncated proteins missing only some

of the repeats will retain function when the main part of the dystrophin is complete. The reading-frame hypothesis is mainly accepted (Florescia et.al. 2004), even if there are exceptions in both BMD and DMD groups.

In some cases DMD patients are reported to have no symptoms of muscle weakness, and several of a cognitive nature. Srour et.al. (2008) describes an 8 year old boy presenting global developmental delay without motor deficits, later evolving into intellectual disability. With a normal neuromuscular function, a mutation in the 3' of the DMD gene was discovered. Kimura et.al. (2009) reports a 9 year old boy with a deletion in exon 74, located between the binding site of α -syntrophin and α -dystrobrevin, showing no signs of muscle weakness, no motor delay and no obvious mental retardation, though this was not tested.

The DMD is clinically expressed primarily among males, but there are evidence of female carrier symptoms. It is suggested that in some cases the normal x chromosome is inactivated, expressing the disrupted DMD gene (ex. Obersztyn et. al.). Guglieri et.al. (2008) found 6 DMD/BMD female carriers (mean age 13.83 years, range 7-20y) presenting with motor and speech delay and learning difficulties. All patients were characterized by delayed speech and ability to walk independently (from 17 to 24 months) in early childhood, and learning difficulties and behavioral problems requiring educational support. (Guglieri et.al. 2008). In a large genetical mapping study of DMD in France 74,9% of the mothers tested positive for mutations, and 24,5% tested negative, indicating de novo mutational events in the maternal genome. In 9 of 1472 proband mothers mosaicism was found (Tuffery-Giraud et.al. 2008). These findings raise the question of identifying females presenting with cognitive dysfunction and delay based on a DMD etiology.

Cognitive functioning in DMD is found to dependent partly on mutational class, size and location (Taylor et.al. 2010), but there is no simple relation between the size of deletion and clinical profile (Anderson et.al.2002, Muntoni et.al.2003). The relative distribution of mutations are changing due to better methods of detecting small point mutations and when selecting patients by stricter diagnostic criteria. Early mapping processes sometimes have difficulties detecting the smallest genomic changes. Identical genotypes are even known to produce different phenotypes.

Most relevant for understanding the cognitive sequelae of DMD are the dystrophin isoforms expressed in cerebellar tissue and different areas in the cerebellum. Mutations in the

distal part of the gene are likely to be associated with loss of all isoforms expressed in the brain, including full length isoforms (Figure 3), and this being a possible explanation to the particularly severe cognitive phenotype. More proximal mutations are associated with a loss of cerebral and cerebellar dystrophins, doing less damage to the brain (Moizard et.al. 2000).

Gene mutations affecting the DP71 and Dp140 regions are associated with the most severe impairment profiles and a higher incident of cognitive deficits. (Perronnet & Vaillend 2010, Wingeier et.al.2011).

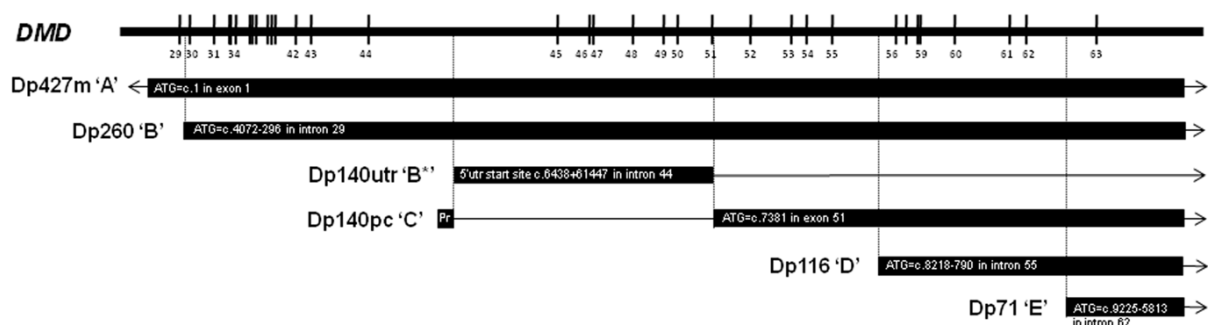


Figure 3 - DMD gene mutations (Taylor et.al. 2010)

The short Dp71 dystrophin is not expressed in skeletal muscles, but are on the contrary expressed abundantly in most non-muscle tissues including brain, retina, kidney, liver and lung. Dp71 is mainly found around brain blood vessels in perivascular astrocytic endfeet, suggesting a role in the brain blood barrier. (Perronnet & Vaillend 2010). It is also detected in the postsynaptic dendrites in adult brain, in granule neurons of dentate gyrus of hippocampus, as well as neocortical regions (thought to play a role in neurogenesis and synaptic plasticity) suggesting an additional contribution in synaptic function (Daoud et.al. 2009). Also found in early embryonic stem cells, embryonic midbrain and hindbrain, perinatal brain at stages of terminal neural differentiation and early embryonic forebrain continuing until adult life, the Dp71 is thought to play a major role in early brain development (Culligan & Oehlendieck 2002).

Several studies have found mutations in the Dp71 region responsible for mental retardation. Five coding sequence changes in the Dp71 sequence were associated with mental retardation, all being translation terminating mutations associated with mental decline. The study included 12 DMD patients, and the changes in DP71 was found among the seven severely mentally retarded patients in the group (VIQ<50 and/or no reading acquisition or global mental deficiency). No mutation was found in Dp71 coding region in two patients with severe cerebral dysfunction or in the five mildly or not retarded patients of this group

(VIQ>70, with delayed or correct reading acquisition) (Moizard et.al. 2000). Daoud et.al. (2009) found in a group of 42 DMD patients with mutations extending to or located in the region of Dp71, all being mentally retarded. In a second group of patients having mutations disrupting all dystrophin products, except Dp71, the majority had cognitive performances either borderline or normal. This will indicate that mutations in the region effecting expression of the Dp71 will lead to mental retardation in DMD, and that mutations affecting Dp427 or Dp140 or both are not sufficient for a majority of patients.

The Dp71 sequence is spanning from exon 62-79, proximally to the cystein-rich terminal end of the gene. Mutations located in this part of the gene are causing all dystrophin products to be affected and clearly has a more devastating effect on DMD cognitive function.

Dp140 is found in large quantities in fetal tissues in the brain, expressed predominantly during fetal development, suggesting this protein plays an essential part in astroglial processes throughout the neuropil during development. (Culligan & Oehlendieck 2002). Mutations affecting the DP140 promoter or protein-coding regions have a larger effect on FSIQ than the mutations affecting the DP140 isoform in the 5'UTR region (Taylor et.al.2010). In a study of 67 DMD boys, it was found that mutations before exon 30 correlated well with IQ ($p<0.003$) whereas there were no correlation with motor function (age of ambulation loss). The same study found that the three participants having mutations after exon 63, i.e. the Dp71 transcript, had severe mental retardation. (Desguerre et.al.2009).

Suggesting that the isoforms DP71 and Dp140 may be related to cognitive impairment (Moizard et.al. 1998, Bardoni et.al.2000, Lee et.al. 2002, Daoud et.al.2009), the presence of moderate but specific memory and attention deficits in almost all DMD patients, regardless of intellectual level, also suggests a role for the full-length (Dp427) dystrophin which is commonly lost in all patients. An important limitation in genotype-phenotype studies in DMD is that germline mutation predicted in blood cannot necessarily predict the presence or absence of isoforms in the brain. At this point, there is no method for in vivo measurement of dystrophin isoforms in the brain (Wingeier et.al. 2011). Measures of dystrophin level in brain tissue are based on post mortem studies or animal models.

Full length dystrophin Dp427 is mainly found in the soma and in postsynaptic densities in brain and cerebellum. Brain regions such as hippocampus, amygdala, neocortex and cerebellum have major expressions of dystrophin, whereas subcortical regions including

striatum, thalamus and hypothalamus, little or no dystrophin is detectable. (Perronnet & Vaillend 2010). The Dp427-C isoform is expressed abundantly in hippocampal granule neurons and some cortical tissue, while the Dp427-P isoform play a vital role in fetal cerebral cortex and maturation of cerebellar purkinje cells.

Several dystrophin isoforms including the full length Dp427-P and Dp427-C, and the shorter Dp71 and Dp140 are expressed primarily during early fetal cerebellar development. The potential destructive elements of this development is not well described, mostly because DMD diagnosis is based on observed clinical developmental findings at a later stage. Depending on which and how many isoforms missing in the developing fetal brain, there will be developmental changes expressed as prenatal cerebellar volume and structure abnormalities (Steinlin 2008), manifesting as high probability for severe mental disability and cognitive dysfunction.

Current hypotheses state that all dystrophins expressed in the brain are likely to contribute to the cognitive and behavioral alterations in DMD (Perronnet & Vaillend 2010), whereas mutations compromising the Dp71 increase the probability of mental disability. Studies of DMD patients have documented dystrophin deficiency in cerebral and cerebellar tissues (Cyrułnik 2008; Kim et. Al. 1995) linking the absence of dystrophin with cognitive impairment (Anderson et.al 2002, Taylor et.al. 2010). There are several ways dystrophin deficiency can affect the CNS. Firstly when dystrophin is lacking or absent in the developing brain affecting cell migration and brain maturation, secondly lack of dystrophin affecting the GABA_A-receptor postsynaptic excitability (Anderson et.al. 2004, Haenggi et al. 2009) and long term cell plasticity (Culligan & Ohlendick 2002), thirdly when dystrophin deficiency causes neuronal death. When full length dystrophin is not present, there are reasons to believe that all those processes are affected in some way.

The reduced density of neurons, deficits in neuron communication and neuronal death are leading to brain dysfunction, especially in the cerebellum. This is confirmed by studies of cerebellar metabolic activity in DMD. PET studies of DMD patients (Bresolin et.al.1994, Lee et.al. 2002) demonstrate patterns of glucose cerebellar hypometabolism and metabolic reduction of cortical associative areas. Of special interest are studies indicating severe involvement of the cerebellum in all DMD patients examined (n=50) and the decreased capacity of these areas (Bresolin et.al.1994). Lee et.al. (2002) are on this ground suggesting links between dysfunction of sensorimotor areas and reduced manual dexterity, temporal

cortical areas and cognitive and behavioral impairment, as well as cerebellum and intellectual and cognitive deficit.

Cerebellar dysfunction in DMD

Looking at the potential cerebellar dysfunction in DMD actualizes comparisons with other groups showing cerebellar dysfunction, here promoted as an example children with lesions after cerebellar tumors and children with dyslexia.

Recent research has expanded the role of cerebellar function, rethinking the cerebellum as being a less important part of the brain, having a motor coordination role only (Beaton & Mariën 2011). The “little brain” possesses 10% of total brain volume, but account for 50% of brain cells (Stoodley & Stein 2011). With a cell intensive structure of Granule cells, Purkinje cells, and deep cerebellar nuclei, the input/output rate of neuro signals from all other brain areas are 40/1, suggesting a monitoring role for motor and cognitive functions alike. Later studies support the cerebellum as a sensory integrating and coordinating unit (Konczak & Timmann 2007) more than a centre of pure motor control (Silveri & Misciagna 2000). There is now solid anatomical support for the “cerebellar cognitive theory” (Engelhardt 2010), placing the cerebellum as a key organ in higher cognitive tasks (Andreasen & Pierson 2008, Schmahmann 2010) smoothing, surveying and automating cognitive processes. Described cerebellar function includes executive function (i.e. planning, sequencing of verbal and visual information (Leggio et.al.2008 & 2009, Molinari et.al.2008)), expressive language (Ackerman 2008), verbal memory (Ben-Yehudah et.al.2007), behavioral and affective regulation, and reading social behavior and intentions (Levisohn et.al. 2003). Cerebellar deficits are also suggested underlying the characteristic mental function in schizophrenia (Andreasen & Pierson 2008, Schmahmann 2010).

Schmahmann et.al. (2009) divides the cerebellum in the motor cerebellum including the anterior lobe (lobules I–V), and the cognitive cerebellum situated within the posterior lobe (predominantly lobule VII). Lateral regions of the superior cerebellum in Lobule VI is suggested to have a motor/non-motor dichotomy role, somewhat similar or corresponding to the cerebral premotor areas, activating motor-related activity, such as planning and preparation. The inferior cerebellum (Lobule VIII) contributes to working memory functions, possibly lateralized by modality of stimulus presentation (Marvel & Desmond 2010a). The diaschisis phenomena refer to the generally observed connections between the cerebral and cerebellar hemispheres are opposite, thus lesions in the right cerebellar hemisphere induces

less activity in the left cerebral hemisphere and vice versa (Baillieux et.al. 2008, Beaton & Mariën 2011). Cerebellar lateralization is proposed to handle verbal information to the right and visuospatial on the left side (Baillieux et.al. 2010). Vermis is the mid structure of cerebellum, associated with a variety of motor, language and behavior functions.

Purkinje granule cells are GABAergic and responsible for cerebellar output via the peduncle structure, connected to most cerebral structures. Interaction between the cerebellum and cerebral areas supporting cognitive functions, go through a closed cerebro-cerebellar loop, known to be of phylogenetical young age and being special for humans (Marvel & Desmond 2010a). One part of this loop system, called the Arnold's Bundle, refers to the fronto-(peduncle)-pontine projection (Engelhardt et.al.2010), connecting prefrontal and cerebellar areas and thought to be the basic structure underlying executive and working memory functions.

In DMD the input to the cerebro-cerebellar loop is thought to be disturbed. Studies of the *mdx* (dystrophin deficient) mouse model for human DMD have detected disruption of the postsynaptic LTP in cerebellar Purkinje cells (Anderson et.al. 2004), proposed to have an impact on cerebellar contribution to cognitive function. The GABAergic input to the Purkinje cells is also reduced in the same model, hence reducing the size and number of GABA_A receptor clusters and total cerebellar output. In *mdx* mice the brain derived neurotrophic factor contributing to neuronal survival, synaptic transmission and cell plasticity is significantly reduced in striatum and pre-frontal areas, affecting storage and restoring of memory (Comim et.al.2009). Findings from the *mdx* mice are disputed, pointing to the difference in syntrophin binding sites (Böhm et.al.2009).

Characteristically cognitive and behavioral patterns are described after cerebellar lesions. Cerebellar Cognitive Affective Syndrome (CCAS) is described as a persistent pattern of executive, visual spatial, linguistic, behavioral, and affective impairments following cerebellar lesions (Mariën et.al.2009). Cognitive changes include impairments in working memory, perseveration, planning, distractibility, and lack of mental flexibility, together with expressive language disorders like dysprosodia, verbal fluency and agrammatism in writing and spontaneous conversation, as well as deficits on visual spatial performance. Affective changes are described as personality changes, disinhibition, disrespectfulness and childlike behavior in adults. Children are described having disturbances of social behavior ranging from irritability to autistic symptoms. These changes are suggested to be consequences of loss

of cerebellar contribution to cognitive functions (Schmahmann 2001, 2010, Tavano et.al. 2007, Steinlin et.al.2003). The postoperative cerebellar mutism syndrome (CMS), also called the posterior fossa syndrome (PFS), is characterized by a number of neurological, cognitive, and behavioral impairments, but especially the limited or absent speech. Frequent observed symptoms also include ataxia, hypotonia, and emotional lability. (Baillieux 2008, Wells et.al. 2008).

Neuropsychological sequelae after cerebellar resection (Levisohn et.al.2000) remind greatly of the described cognitive profile of the DMD children. Wingeier et.al. (2011) even states that “The neuropsychological profile of our DMD patients is similar to those of patients with focal cerebellar lesions”. There are limitations interpreting and comparing findings from childhood lesions and neurodevelopmental issues of DMD. Firstly there is a possibility that the structure of cerebellum in the two groups differ significantly as a result of disturbed early neurodevelopment. Then there are possible functional differences due to the abnormal expression of dystrophin, not present in the cerebellar lesion group. The DMD group will present with a more complex pattern of dysfunction interacting with developmental processes.

Dystrophin deficiency has also proved to affect other brain tissues depending on GABAergic transmission, inducing the amygdala local inhibitory neuronal circuits (Sekiguchi et.al. 2009), reducing metabolic activity in cortical sensorimotor area, temporal neocortex, and medial temporal structures (Lee et.al. 2002), and decreasing activity in the hippocampal granule cells (Del Tongo et.al. 2009).

COGNITIVE FUNCTION IN DMD

There is a large variability of severity in expression of this disorder, from cognitive abilities within normal range and above, to profound cognitive disability. About 1/3 of DMD patients are showing an IQ below 70 (Bresolin et.al. 1994). The reading ability recorded in this group is clearly biased by the large subgroup of mentally disabled. Still among DMD boys within normal abilities half show moderate to severe reading difficulties (Hendricksen et.al. 2006), compared to the 3-10% incident of dyslexia in normal population. Compared to their siblings, DMD boys have significantly poorer academic achievement scores (Hinton et.al. 2004). No studies have confirmed progressive cognitive decline in either diagnostic groups.

Some studies have confirmed the general ability level correlating with the DMD gene mutation, but not with motor disability (Desguerre et.al. 2009, Taylor et.al. 2010). Taylor et.al. (2010) tested 62 DMD boys with neuropsychological tests, correlating mutational class, size and location, including cumulative loss of dystrophin isoforms, with standardized measures of intelligence. Suggesting that the risk of cognitive deficits is a result of a cumulative loss of dystrophin isoforms expressed in the CNS. They conclude that there is a correlation between FSIQ results with the location of the dystrophin gene mutation, and that the site of the mutation is a determinant for risk of cognitive deficits. Within the group of BMD patients there have been no findings of such a relation. However, Young et.al. (2008) concludes with a significantly higher frequency of learning difficulties within the BMD group compared to the normal population, despite normal intelligence.

The connection between FSIQ and mutation location is not replicated in all studies and not for mutation size, all though the number of mutations add to the risk of hitting a “hot spot” important for cognitive functioning. There are also clear exceptions clouding this connection. A pair of DMD twins with a nonsense mutation in exon 44, as well as siblings with a duplication in exon 17, differing in their full scale IQ by 1.5 SD, even though they shared the same genetic defect, the same environment and medical and social support (Wingeier et.al. 2011). Further investigations of this connection will be a future challenge.

DMD boys as a group are described having sub-average cognitive capacities (Hendriksen et.al. 2006) and lower verbal IQ scores than performance IQ scores (Hinton et.al. 2007, Billard et.al. 1998). In addition to delayed language development (Cyrulnik et.al. 2007), described cognitive deficits include specific learning difficulties, working memory impairment, general executive function deficits in addition to generally reduced level of ability (Cotton et.al.2001). The milder Becker muscle dystrophy (BMD) is associated with less profound muscle weakness and general ability level within normal range.

Traditionally broad assessments of cognitive function using Wechsler’s intelligence tests (WPSSI, WISC-III/R and WAIS-R) often fail to consistently characterize the cognitive function of this group (Kjærgård et.al. 2006). When using Raven’s Colored Progressive Matrices as a measure of intellectual ability in a study of 20 DMD, the DMD group fell within normal range (Wicksell et.al. 2004). Findings vary from 1 SD below normal level (Bresolin et.al. 1994) of IQ to results within normal range. In several studies the IQ is normally

distributed, but tend to be shifted towards the left side. The distribution of IQ scores in DMD samples is often broad (n=25, IQ span 50-130, mean IQ 88) (Wingeier et.al. 2011).

Heterogeneity in mental abilities in addition to small samples in study group will be a large factor in explaining non-conclusive and variable findings in the DMD group. Control groups discarding mentally disabled will not compare well to the DMD group with 35% characterized as being mentally disabled, also disregarding the specificity of the DMD group.

A research challenge is reliance on WISC-III and other measures of general intelligence, when there are obvious specific difficulties with verbal working memory that can interfere with this measure. IQ alone may fail to indicate the extent of cognitive impairment in brain-damaged or learning disabled individuals. Additionally, IQ tests generally rely on eye-motor skills to assess non-verbal cognition and for DMD patients these tests may be unreliable because of the patients' declining abilities to perform rapidly on tasks with a motor component. (Dorman et.al. 1998) Reliability will also be compromised in Wechsler scale III with locally undescribed adjustments made for DMD patient's individual motor deficits and other difficulties. (Kjærgård et.al. 2006, Wingeier et.al. 2011). There is also a questions of validity to the WISC III compared to the latest version WISC IV when it comes to marginal groups, especially children IQ<70. Few marginalized children are recruited to norm groups and there are few studies of particular profiles for groups with different disabilities. An observation worth considering is that some children who tested as disabled with an IQ score below 70 in WISC-III are over the limit and not mentally disabled in the latest version of the test.

The lower verbal vs nonverbal performance is confirmed in different studies (Bresolin et.al. 1994, Cotton et.al.2001) and not found in other studies. Young et.al. (2008) found in 23 BMD males aged 6.0-43.2 years a mean VIQ of 98.1 (SD 23.7) and PIQ 92.9 (SD 20.8), measured by Wechsler's scales (WISC-III and WAIS-R). Full scale IQ for the total group was normally distributed with mean 95.6 (SD 23.3), not significantly different from the normative mean value. In the subgroup of children (n=16, FSIQ 93.8, SD 20.5), subtests gave a profile of children's strengths and weaknesses, showing 6 children even with significant strengths in verbal subtests. Several children showed significantly lower performances in verbal subtests of arithmetic and reasoning, indicating impairment in verbal working memory, short-term memory and sequential processing. They conclude that BMD males have a high frequency of learning difficulties despite normal intelligence. Wingeier et.al. (2011) found no significant

difference between verbal and performance IQ in a group of DMD patients (n=25), no correlation between IQ. Cotton et.al. (2001) found DMD VIQ scores to be somewhat lower than PIQ, but the difference were not clinically significant.

Despite disagreement on the discrepancy between verbal and nonverbal IQ in DMD patients, there is a consensus of “some” common language problems in the group. As mentioned above the tests for general ability are too general as to assess the specific difficulties this patient group is struggling with. As to the left shift of the normally distributed curve of general ability, this is quite intriguing taking the huge genotype heterogeneity in this group into consideration. Statistical significance is not always the most useful tool for understanding individual characteristics, and there are clearly few test tools available for assessing the kind of difficulties found in the DMD group.

The rarity of the DMD also makes it challenging to locate and recruit precise and representative selections for research. Many studies include boys with a huge age span, placing preschool children and adults in a common DMD group, as well as mixing different subtypes, and levels of mental ability, excluding subtypes with non-typical or absent symptom picture. Taken the huge heterogeneity in both genotype and phenotype this is problematic and reduces the value of findings, especially for individual therapy purpose.

Pattern of neuropsychological defects

Regardless of intelligence scores, DMD patients seem to have a specific pattern of neuropsychological defects (Bresolin et.al. 1994, Wicksell et.al. 2004, Hinton et.al. 2004, Wingeier et.al. 2011). Wicksell et.al. (2004) compared a group (n=20, mean age 9y5m, SD2y2m) of DMD boys with a control, using specific neuropsychological tests to map performance in sensory storage, short-term memory, information processing/learning ability and long-term memory. Long-term memory and learning ability is found to be relatively normal, while short-term memory is significantly below normal in the DMD group. The DMD group showed major difficulties on the verbal fluency test. The conclusion was that the specificity of cognitive deficits is not either verbal or visuo-spatial, but pointing to factors underlying short-term memory and executive function.

The relatively intact visuo-spatial performance is confirmed in different studies (Wingeier et.al. 2011). Performance on the “block design” task in Wechlers tests (WISC-III) is often showing as an individual strength in the DMD groups tested.

Descriptions of cognitive function in DMD often states some kind of linguistic problem, but the terms and concepts vary. Cyrulnik et.al. (2008) compared a group of preschool DMD children (n=20, age span 4-6y, mean age 4.9y) with a group of unaffected siblings. 35% of the DMD group scored more than 1,5 SD from the population mean attention, memory and expressive language. The language deficits are not described as being of a dysphasic nature. Language problems are characterized by a delay in language acquisition and deficits in narrative/linguistic/reading skills (Hendricksen et.al. 2006, Marini et.al. 2007). The most common description includes verbal working memory, referring to the ability to hold on to verbal information with the purpose to further process by manipulation, meaning comprehension or storage in long term memory.

Verbal working memory

Baddeley (2006) describes working memory in a four component theoretical model, including a domain general central executive responsible for control and coordination of short time information and long time memory, linking to control processes like attention, switching between strategies, coordinating performance on dual tasks, updating and inhibiting irrelevant information (Holmes et.al. 2010).

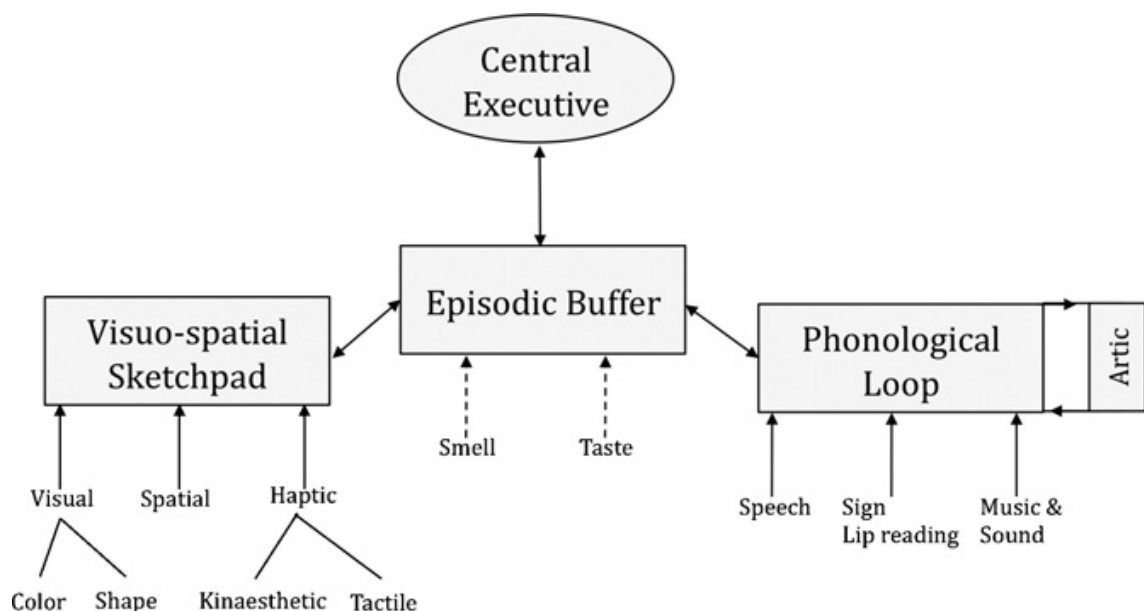


Figure 4 – Model of working memory (Baddeley et.al. 2011)

Two slave systems deal with domain specific information and the storage of visual/spatial and linguistic material. The phonological loop handles linguistic material, and the visuospatial sketchpad deals with visual information. Information from these components

is integrated with long time storage in a fourth component, the episodic buffer (Baddeley 2000, Baddeley et. al. 2011), also suggested as a central executive working memory (van Daal et.al. 2008).

The working memory concept is referring to both a system for temporarily storage of information and the ability to manipulate this information for further use in complex tasks as comprehension, reasoning and learning. Working memory is an important mental workspace used in everyday cognitive actions as well as more specialized high order mental activities as mental arithmetic and manipulation of thought strategies. The storage capacity is limited, but the systems rely upon long time memory, automatic procedures, learned strategies and associations to familiarity. Working memory processes include the ability to hold on to relevant information, and regulate controlled processing of this information in relation to a task or a goal. Working memory capacity reflects the ability to maintain relevant information in a highly active state, long enough to reach a goal or to finish a task, and is a valid predictor for attentional control (Kane et. al. 2001).

The episodic buffer is presented as a consequence of limitations to the phonological loop and visuospatial sketchpad when dealing with serial tasks, sorting or sequencing. This unit is suggested as a general rehearsal unit involving sequential attention (Baddeley 2000) and binding of features (Baddeley et.al. 2011). “It’s major function is binding together sources of information forming integrated chunks” (Baddeley et.al. 2011). How binding are maintained and the effect of attentional load on this system are yet to be investigated.

Sorting relevant information includes remembering something, ignoring other competing stimuli or irrelevant information, and processing the relevant information while holding on to the task, repressing competing memory traces (Swanson 2006). Sorting and holding on to information involves several controlled processes. Firstly controlled attention is thought to have a crucial role in working memory capacity. Controlled attention defined as the ability to hold on to relevant information when distracting or interfering stimuli is present (Engle et.al. 1999). Then there are processes of binding, grouping, sequencing and truncating perceptual input. Making sense of and systematizing information effectively will enhance memory capacity. Phonological coding and repeated rehearsal refreshes the memory traces. (Swanson 2006). Ex. in order to remember a list of words – puma, pumps, pumpkin, snake, sneakers, snail – there are useful truncation similarities within the pum-words and the sn-words, and semantic category relations between the animal words and the clothing words.

The Baddeley model, though a theoretic model, has shown to be applicable in clinical settings. Van Daal et.al. (2008) tested the working memory in a group of 5-year olds showing severe language impairments. Operationalizing the concepts of the working memory model, all children showed difficulties with central executive and phonological aspects of working memory. They found that phonological memory predicted phonological abilities, whereas central-executive memory predicted lexicalesemantic abilities, and visual memory predicted speech production abilities. In addition phonological abilities also predicted syntactic abilities (van Daal et.al.2008). These findings indicate that working memory deficits and language impairment factors are related.

Operationalizing the concepts of the working memory is not a straight forward procedure, suggesting a careful interpretation of the results. The construct validity of digit span tasks, word span and sentence span task are questioned, asking for clarity in connection to reading and working memory concepts. Even so; damage to the cerebellum gives sequelae affecting abilities in the working memory domain, suggesting a relation between the general understanding of the concepts and neural systems. The cerebellum has been suggested having a major role during phonological rehearsal, controlled attention and sequencing, and verbal working memory especially (Misciagna et.al. 2009, Marvel & Desmond 2010a).

Executive function

Prefrontal cortex has been well established as the centre of attentional control, inhibition and other executive function. Recently the basal ganglia and cerebellum is suggested to play a major role in multitasking and response inhibition, central features of executive functioning (Thoma et.al. 2008) as parts of a fronto-subcortical-cerebellar network. Marvel & Desmond (2010) studied the cerebro-cerebellar load activity due to executive verbal memory tasks. In a fMRI study 16 subjects completed two versions of the Sternberg verbal memory task. Presented initially with two or six target letters, in the “match condition” the subjects decided if a single probe letter matched the target letters. In the “executive condition” the subjects created the probe letter by counting two letters forward alphabetically (e.f.g => h). Neural activity during the tasks was compared with initial activity. There were four main findings. Cerebro-cerebellar load increased significantly as a function of executive load, and cerebro-cerebellar activity predicted performance success on the executive task. Marvel & Desmond have drawn the conclusion that cerebellar dentate activity was related to encoding and retrieval activities under demanding executive working memory tasks. Secondly

the topography of the cerebellar dentate activity varied throughout the task, presuming to reflect the different phases of encoding, maintenance and retrieval. The encoding phase initiated the dorsal dentate, and the ventral dentate was activated during retrieval presuming to reflect the process of requiring stored information in the “executive condition”. (Marvel & Desmond 2010). This and other studies are pointing towards a close connection between cerebral and cerebellar areas, especially when it comes to executive function. In DMD the output purkinje cells of the cerebellum are found to be less excitative, decreasing the signals though the dentate and the cerebro-cerebellar system. Giving the above mentioned task to DMD boys, they would probably fail heavily and not being able to mobilize resources in the executive condition.

Important for understanding the process of reading, is verbal working memory and associated executive processes to retain attention and attentional shifts, and enhancing fluency, rehearsal and updating. Attentional control is thought to be crucial in fluent reading, inhibiting concurrent stimuli and performing attention shifts, both in continuous visuospatial processing, phonological rehearsal and collection of meaning. Verbal working memory is also divided into the actual memory for items – i.e. verbal memory span, and the underlying perception of item sequence and visuospatial interpretation.

Verbal fluency

As a neuropsychological measure of executive function, verbal fluency is often tested asking the person to say as many words as possible starting with a certain letter or belonging to a category. Switching between categories or alternating letters will put even more strain to the executive control of working memory, holding on to the task while generating output relevant to shifting contexts. Cerebellar activation to these functions is evident. When persons doing verbal fluency tasks are compared to controls, right posterior cerebellar and left prefrontal activations are detected. The right cerebellar activation is seen when novel verbal information is presented, and will decrease with known information. (Desmond & Marvel 2009). The cerebellar contribution is thought to be especially important in learning and dealing with novel material.

DMD patients are struggling with verbal working memory, both sequence and decoding, and thereby verbal memory span. Bresolin et.al. (1994) suggests that DMD patients have a disability in higher syntax verbal mediated processes. They also explain the impairment of productive language (measured by the Chicago Word Fluency test) by the

deficit of semantic memory, as part of the short-term memory. Hinton et al. (2004) propose that the “core” deficit is the limited verbal span associated with DMD, which can influence on phonological-decoding skills. Wingeier et.al. (2011) found DMD patients having significant difficulties with ”phonemic verbal fluency” of the Regensburger Word Fluency Test (RWT), producing as many words as possible starting with letter “s”. Most patients in this study showed severe verbal short-term memory deficits regardless of full scale IQ score. Hinton et.al. (2007) found consolidation and retrieval to be intact despite limited capacity for verbal span. This implies a defect in the process preceding the consolidation phase.

The Studies of sequelae from cerebellar tumor resection in children also points to impairments in executive function including planning and sequencing, visual-spatial function, expressive language, verbal memory, and modulation of affect (Levisohn et.al. 2000, Brahmabhatt 2007). Decreased cerebellar volume is found in different groups struggling with attention, working memory, sequencing and planning, for instance dyslexia (Nicolson et.al. 2001, Stoodlay et.al. 2006), fragile X syndrome (Steinlin 2008), ADHD, autism spectrum disorder, schizophrenia, and very premature babies (Desmond & Marvel 2009).

Attention and cognitive flexibility are core functions in verbal fluency tests switching between conditions or categories. Swanson (2006) suggests controlled attention (i.e. updating, switching) to be the crucial component of the central executive in reading difficulties. His studies implicate deficits in executive processing for children with reading difficulties, particularly referring to controlled attention. Involvement of central executive processes is inferred from three outcomes: problems inhibiting irrelevant information (monitoring), poor performance on divided attention tasks and lower performance with concurrent verbal and visuospatial tasks. (Swanson 2006).

Cerebellar contribution to cognitive flexibility tasks is documented both in mouse models and humans alike. Dickson et.al. (2010) observed mice with developmental cerebellar purkinje cell loss to struggle with behavioral flexibility in an operant conditioning task, doing significantly more perseverative errors than controls. Bilateral cerebellum is observed activated by a card sorting test (Wisconsin Card Sorting Test – WCST) in addition to a network of cortical and subcortical activations (Desmond & Marvel 2009). The lack of cognitive flexibility and perseverativeness in cerebellar dysfunction calls for a comparison with autism spectrum disorders. Cerebellar atrophy is frequently observed in autism, and especially selective loss of Purkinje cells. Reduced GABAergic activity is also associated

with autism. (Rout & Dhossche 2008). Some DMD patients lack functional dystrophin isoforms present in purkinje cells in the cerebellum, compromising the GABA-A receptors however it is yet to be discovered if these are the same showing a autism spectrum symptomatology.

Verbal memory

In the simplest form, verbal working memory is about holding on to verbal information, i.e. a name or number, long enough to put it into use like dialing a telephone number or finding a location on a map. This task will need updating via the phonological loop through repeating and rehearsing the information as long as it takes to arrive at the point where the information is operated further. The central executive processes are hypothesized to be responsible for the many ways of manipulating the information, but the verbal memory span will limit the amount of information available for this processing.

Cerebellar activation is observed in both simple verbal memory tasks and manipulating tasks alike (Desmond & Marvel 2009). Cerebellar patients show a variety of deficits in executive function and verbal and visuospatial memory and seem to be more impaired in delayed working memory tasks (Koneczak et.al. 2007). Bilateral cerebellar activation is documented by fMRI studies of healthy volunteers during verbal working memory tasks (Ravizza et.al. 2006). Kirschen et.al. (2008) found that damage to left hemispherical lobule VIII was associated with reduced digit span to auditory stimuli, indicating that damage to this lobule may affect phonological storage.

Several studies have revealed a limited verbal storage capacity in the DMD group. Donders & Taneja (2009) found delayed memory for verbal and nonverbal contents alike to be the most striking difference between DMD boys and their unaffected siblings. Hinton et. al. (2006) found that DMD boys have limited capacity for verbal span but are not impaired in consolidation or retrieval. “The participants with DMD performed significantly more poorly on the Recalling Sentences subtest of the Clinical Evaluation of Language Fundamentals (CELF-3) than their siblings. In the DMD–sibling comparisons, poorer performance was also found on subtest Concepts and Directions. Accurate performance on both tests requires listening to and replicating a specific sequence of verbal information. These data support the hypothesis that children with DMD have compromised immediate recall for increasing spans of verbal information.” (Hinton 2006)

Verbal working memory is a sensitive neuropsychological marker, which might also account for deficits in other cognitive tests (Wingeier et.al. 2011). In learning the phonological structures of new vocabulary items, children with poor verbal memory show an impairment in this process and need more time to acquire new items (Alloway 2006). Poor verbal working memory is also associated with specific learning difficulties in complex cognitive tasks as reading and arithmetic. This may be a reason for DMD subgroups having difficulties in general ability tests, and account for their general poor academic performance.

Sequencing – the cerebellar model.

The cerebellum has been suggested to play a role in strengthening memory traces, like phonological rehearsal, comparing patterns and integrating auditory, phonetic and articulate representations, correcting and updating sensory information (Leggio et.al. 2011). The order of sensory information will be crucial for extracting meaning and forming contextually customized output, leading to the cerebellar contribution to implicit sequence learning.

One hypothesis is that sequence detection is one of the main cerebellar contributions to cognitive function Molinari et.al. (2008). Detecting and generating sequences may be a key to understand the basic cerebellar function in cognition. The cerebellum intervenes whenever a feed-forward control is needed in order to identify patterns of sequence detecting meaning or forming associations. Leggio et.al. (2008) did two experiments with sequencing in cerebellar patients. In the first study patients (n=77) with known and strictly cerebellar lesions were assigned the Picture Arrangement subtest from the Wechsler Adult Intelligence Screening test (WAIS-r). The first group was divided into subgroups based on localization of the lesion. The cerebellar lesion group as a whole presented a preserved general cognitive pattern. There were no differences detected between the subgroups, but compared to a control group, the combined performance of the cerebellar patients group was significantly lower ($p < 0.001$). Even though all subgroups performed within a normal range, all scores were lower than the control (Leggio et.al. 2008). The second study (n=45) offered three kinds of stimuli to sort; verbal – building a story with sentences, visuospatial – constructing a puzzle of an abstract pattern and behavior – sorting pictures of people in social interaction. A connection was found between lesion side and characteristics of the material. Patients with left cerebellar lesions struggled only with pictorial material, whereas patients with right side lesions performed worse on verbal based material. All cerebellar patients showed impaired performance in cognitive sequencing.

The Picture Arrangement task is considered to assess the capacity to process sequencing of scripts – behavioral, action and semantic alike. Script-sequencing has been previously associated with frontal lobe and basal ganglia circuits. Leggio et.al. (2011) suggest that cerebellar involvement in this function is more prominent, involving sequencing of all kinds of modalities, even placing cerebellum as the key structure for preparing responses to predictable sensory events (Leggio et.al. 2008).

Sequencing plays an important role in implicit learning and nonverbal communication as well. Folia et.al. (2008) found that an implicit acquisition deficit is related to sequence processing, and most likely is related to sequence complexity. Liebermann (2000) proposes that implicit learning processes based on sequence understanding underlie social intuitive behavior. This is supported by review of relevant neuropsychological studies of Huntington's and Parkinson's disease and a conceptual correspondence between nonverbal communication and implicit learning, concluding that the caudate and putamen, in the basal ganglia, are central components of both intuition and implicit learning. Non-verbal communication is central for social cognition and action. The temporal and spatial sequences of cues that compose facial, vocal, and gestural cues are associated with internal states of emotion and attitude. Within the DMD group, facial recognition is generally poor. The consequence of not being able to learn or to comprehend these non-verbal communication cues and the specific meaning of a sequence will in many cases cause behavior categorized within an autistic disorder spectrum, also widely documented within the DMD group (Wu et.al. 2005, Poysky 2007, Hinton et.al.2006 & 2009, Hendriksen et.al.2010).

DMD boys struggle generally with serial memory tasks. 10 DMD boys (age range 6y6m-16y1m, mean 11y1m) were tested with a memory test, where 8 positions were filled with black line drawings (from the Peabody Picture Vocabulary Test). Their task was to remember the pictures placed in positions from left to right, one by one disclosed and hidden, and place a target item in the right position. Compared to an age matched group with no known disabilities, the DMD group did more errors (169 errors compared to 74 in the control group) and larger displacements than the control (mean 2.3 displacement positions to 1.9 in the control). The two groups had nearly identical performance on the recency portion of the task, but performed less than half of the control group on first half (primacy portion), suggesting that DMD patients are impaired in ability to retain information in immediate memory when new information is presented (Anderson et.al. 1998). Verbal working memory

was studied further by Hinton et.al. (2000) noting that the DMD had a reduced performed compared to their siblings on tests of digit span, comprehension, and story memory. This was true regardless of degree of cognitive involvement in the DMD subjects. They had the most difficulties with tests requiring attention and ability to hold on to and work with aurally presented information. An example is a young DMD boy presenting with severe verbal short-time memory difficulties, not able to reproduce aurally information unless there was a very short span from given target to response. He was not able to repeat anything from a delayed reading of a digit row with more than two digits, whereas rapid reading of four items gave a correct response.

In a test of working memory the subject is to remember, manipulate, and repeat back a string of digits; comprehend, consider, and respond to a linguistically complex question; and listen to, process, and reconstruct a short story. The cognitive profile associated with DMD has areas of cognitive deficit that appear to be related to deficient verbal working memory and auditory comprehension skills (Hinton et.al. 2000). According to the working model by Baddeley et al. (2000) these functions are related and bound together by a central executive, whereas Hinton et.al. (2000) is suggesting that DMD performance is compromised by the “phonologic loop” necessary for optimal development of verbal working memory.

There is little doubt that cerebellar activation is present in most working memory processes, from simple rehearsal to executive functions like planning, attention shift and underlying features like timing, sequencing and learning. Both fMRI and lesion cerebellar studies suggest a significant cerebellar contribution to verbal working memory (Ravizza et.al. 2006) most relevant for understanding the DMD cognitive characteristics. In most adult cerebellar lesion patients the digit span is relative preserved, quite contrary to the DMD profile. The largest difference between these groups is the developmental factor. Dystrophin isoforms Dp427-C and Dp427-P would normally be distributed in Hippocampus and Purkinje cells in the cerebellum respectively, contributing to higher degree of postsynaptic density (Culligan & Ohlendieck 2002), and important in early brain development and maturation. In DMD patients these dystrophins are often compromised, causing reduced cell efficiency and density in these structures, and by thereby loss of capacity and function. The cognitive decline seen in the DMD group compares well to other groups with congenital cerebellar deficits.

Cerebellar development - Neurodevelopmental perspectives.

The development of the cerebellum is especially rapid from 24 weeks to 40 weeks of human gestation, where the volume increases 5-fold. GABAergic neurons migrate to form the roof nuclei, the Purkinje-cell layer, and the molecular layer. Cerebellar abnormality in survivors of premature birth is likely to depend on a combination of destructive and impaired trophic or maturational mechanisms (Volpe 2009).

Children with congenital malformations of the cerebellum show severe delays in development of cognitive, linguistic, affective and motor, especially when phylogenically older parts of the cerebellum, like the vermis are affected. (Steinlin 2008). Their symptoms resemble those associated with the CCAS, affecting the development of all abilities. Language disabilities are present in all these patients (Tavano et.al. 2007), underlining the role of the cerebellum in supporting language processing mechanisms, production and comprehension alike. Children with cerebellar hypoplasia, Dandy Walker and Joubert syndromes and other congenital conditions (ex. Down's, William's, Fragile X) have shown to produce abnormal cerebellar morphology and volume with concurrent cognitive and affective effects. Other pre- and perinatally acquired cerebellar abnormalities include dysmorphology as an effect of alcohol exposure and a variety of lesions in preterm children. (Steinlin 2007).

In DMD children maturational factors are thought to be disturbed, especially with specific dystrophin isoforms such as Dp427-P and Dp140 are compromised (Wingeier et.al. 2011). Other mechanisms compromising cognitive development in a non-progressive way have yet to be discovered.

Cerebellar hemorrhagic injury in premature infants is associated with significant risk of adverse neurodevelopmental sequelae (Limperopoulos et.al. 2007). Cerebellar hemorrhage or infarction occurs at a high rate in the very premature infant, and impaired cerebellar growth and injuries associated with deficits in cortico-cerebellar neural connections add to common cerebellar prenatal injuries. Cerebral parenchymal brain injury is found to be associated with impaired cerebellar gray and white matter development, suggesting that early life direct or secondary cerebellar injury or underdevelopment plays a role in the long-term cognitive, behavioral, and motor sequelae among premature infants. (Limperopoulos et.al. 2005). Evidence from the premature group also shows that cerebellar lesions lead not only to motor deficits, but to significant cognitive, attentional, social and psychiatric manifestations including autistic behaviors (Volpe 2009, Schmamann 2010). Limperopoulos et.al. (2007)

found a high prevalence of significant deficits in communication (both receptive and expressive), and social-behavioral function in a group (n=60) preterm infants (gestational age < 32 weeks).

Cerebellar abnormality is commonly found in premature infants with very low birth weight (Volpe 2009, Messerschmidt et.al. 2005). Neuropathological analysis of 41 premature infants identified neuronal loss in the dentate nucleus and the cerebellar cortex in 25–30% of the infants. MRI studies that analyzed pontine size, both pontine diameter and cerebellar volume were reduced in premature infants with Periventricular Leukomalacia (PVL) (Volpe 2009). PVL is one of the most common preterm ischemia injuries, present in varying degrees in about half of very low-birth-weight often leading to cerebral palsy.

There are often few obvious behavioral difficulties observed as a result of limited cerebellar resection in young children, and subtle cognitive decline, often within normal range, in adults suffering cerebellar lesions Leggio 2011, Marvel & Desmond 2010a), suggesting that the rest of the brain is able to adjust and function well without the cerebellum (Boer & Parsons 2003), this contrary to cerebellar prenatal lesions. The rapid recovery may depend on the partial functional re-activation of a “redundant” cerebral center which remained intact. (Fabbro et.al. 2000). These redundant centers probably need to develop in order to compensate for deficits caused by cerebellar lesions. Findings in *mdx* mice show alterations involving the cortico-spinal system and cortical interneurons, and the hippocampal inhibitory synaptic transmission, suggesting a cortical rearrangement of cortico-cerebellar networks following dystrophin deficiency in this model (Minchiacchi et.al.2010).

After specific cerebellar injury the brain will restore many of the vital functions after a short time, i.e. there are cerebral processes that are able to take over or partly compensate for some of the lost cerebellar function. The important view of the cerebellum being a central but not single part of a cortico-cerebellar network – will be able to robustly restore or rebuild function despite some cerebellar dysfunction. This is a fascinating view that will give hope for possibilities of strengthening the existing robustness instead of focusing in on the “lost” parts. This will make a huge difference for practioners working with DMD patients and other cerebellar patients in everyday tasks.

READING DIFFICULTIES IN DMD

Reading is a fundamental skill in modern literate society. School curriculums are devoted to reading or reading related activities. Identifying children at risk for reading difficulties and finding strategies addressing the cause or compensating for dysfunction will be crucial. Reading abilities among DMD patients are reported to be generally poor. About half of the DMD boys did very poorly on reading tests, characterized as having limited reading skills (Liebowitz & Dubowitz 1981, Billard et.al.1992, Dorman et.al. 1998). Hendricksen et.al. (2006) concludes that DMD males are at higher risk for developing reading problems. In a study of the reading capacity in 25 DMD patient (age 8-12, mean age 10.1y) they found about half of them showing moderate to severe reading difficulties and 10 within normal range, whereas the reported incidence of dyslexia in a normal population is 3-10%. Subgroups of DMD have been reported having a “common pattern of deficient auditory processing and academic skills reminiscent of some types of dyslexia.” (Dorman et.al. 1988).

There is a tendency to treat dyslexia as a unitary syndrome, looking for one single, underlying cause. With research progresses, the list of subgroups is increasing in length. The process of reading requires automated word decoding skills, which in turn activates a broad list of abilities from visual recognition of single letters to extracting meaning from sentences in a text. In a neuropsychological perspective there are a variety of skills needed to support the process of reading, and potentially a long list of possible neurological dysfunction preventing efficient reading. Focusing on the learning perspective, dyslexia is about deficits in the process of acquiring reading skills, both as a potential result of executive based problems and automatization deficits (Nicolson & Fawcett 2006). Dyslexia is also associated with a number of language based deficits. The phonological core-deficit hypothesis (Eden & Flowers 2009) represents one of the most accepted explanations for dyslexia, focusing on phonological awareness and phonological retrieval and recoding – i.e. verbal working memory deficits. Children may also exhibit other language-related process deficits, or even reduced executive function or imaginary skills hampering fluent reading.

Reading disorders/difficulties are defined as specific processing deficits reflecting biological, neurological and/or constitutional factors, and not a result of general lowered intellectual abilities or lack of learning opportunities. (Swanson 2006, Eden & Flowers 2009). It is characterized by difficulties with fluency and accuracy in word recognition, and poor decoding and spelling abilities. Consequences of these difficulties are problems with reading

comprehension, which in turn can lead to fewer reading experiences, reduced vocabulary and knowledge acquisition. (Eden & Flowers 2009).

The dyslexia definition (as stated in DSM-IV and ICD-10) based on IQ discrepancy has its fundament in an idea that specific difficulties occur in absence of poor general cognitive abilities. Defined as a discrepancy between general ability measures and reading skills, the diagnosis criteria are effectively ruling out those children with low levels of general abilities even though this group struggles equally with reading. There is a debate of this view, considering a dual effect of reading difficulties and the measure of general abilities. Savage (2008) found that children with low IQ did not differ in performance on cerebellar tests (Barth et.al. 2010) or speeded response inhibition measures compared to children with developmental dyslexia, indicating that dyslexic children and children with low IQ are not different in their poor reading (Savage 2007). This raises the question of using the dyslexia concept in DMD, where 1/3 has IQ below 70 and half of the group presents with reading difficulties, leaving about 20% potential members of the dyslexia subgroup. A larger number will struggle with reading anyway, and there is a clinical gain from considering the common risk factors in cognitive function for the group as a whole, recognizing the possibility of common factors with general ability measures, regardless of inclusion in any dyslexia subdiagnosis.

There is also a tradition of measuring reading skills in discrepancy of “reading age” and “chronological age”. The verbal IQ is considered a part of the general ability measure, also predicted to be low when the reading skills are sparse. There is poor correlation between nonverbal IQ and reading skills in normal populations, indicating that correlation of general ability and reading scores is not expected (Eden & Flowers 2009).

An alternative approach to diagnosing dyslexia is the Cognitive Marker approach, stating that affected individuals should be identified by underlying cognitive deficits, rather than behavior on psychometric tests (Snowling 2000). By comparing reading comprehension with listening comprehension, the children with broader oral problems are distinguished from those with particular problems with written text. A discrepancy between these measures will identify those children with relatively pure phonological based reading difficulties. (Bishop & Snowling 2004). The Dual Route model of reading is a dual route cascaded model of visual word recognition and reading aloud. Within this framework reading impairments can origin from deficits in either lexical or nonlexical processes, or a combination of the two (Ziegler

et.al. 2008. Investigations of dyslexic children reveal a complex pattern of phonological, phonemic, and letter processing deficits and no single explanation nor profile (Ziegler et.al. 2007). Procedural, declarative and sensory “neural systems” contribute to the process of reading (Nicolson et.al. 2010), giving room for a variety of explanations and dyslexia hypotheses.

The Double Deficits theory of dyslexia suggests that the core deficits are phonological processing and verbal fluency skills. The Visual attention span theory acknowledges the deficits in rapid naming skills and phonological processing, proposing two types of reading procedures relying on visual attention shifts; global versus analytic (Bosse et.al. 2007). Shifts from a letter focus to whole words to sentences and meaning illustrates the executive demands in reading, embraced by this theory. Children with developmental dyslexia often have difficulties with the global mode, preventing the transition from letters to meaning. Where fluent readers understand with a glimpse in a one step global analysis, dyslexic readers stay at the letter-by-letter analytic level losing the bigger picture. Building bottom-up heuristics allocates resources for increased processing capacity.

The anchoring-deficit hypothesis builds on the attentional deficits theory, focusing on ineffective bottom-up driven attentional mechanisms and lack of benefit dyslexic individuals seem to have from stimulus-specific repetitions, accounting for phonological, working memory, visual and auditory difficulties (Ahissar 2007). Fluent readers are better at grasping a context either presented previously in a text or suggested by new clues, anchoring new stimuli to this context, while individuals with dyslexia often miss these anchoring opportunities.

The phonological processing deficits include the sensitivity for individual sounds of speech, having difficulties consciously perceiving, blending and manipulating spoken sounds. (Beneventi et.al. 2010). Investigating the ability to process simultaneous and sequential visual information, dyslexic children was found to perform significantly poorer than control in simultaneous processing, but not in serial processing skills (Lassus-Sangosse et.al. 2008). In addition, children with reading difficulties struggle with attentional demanding memory tasks. fMRI studies of dyslexic children (n=12) performing the n-back task, showed less activation compared to control, indicating processing difficulties with this demanding working memory task (Beneventi et. al. 2010). Swanson (1993) administered concurrent tasks for groups of RD children and normal achievers. The two groups sorted blank cards, pictures of nonverbal

shapes and cards with pictures of items with semantic categories (vehicles – car, bus... clothing – dress, sock) – and at the same time they were to remember digit strings (2, 6, 1, 9, 5, 3...). The RD group differed generally in achievement from the normal group in the way they handled these concurrent tasks. By manipulating the level of difficulty, Swanson found that placing more demand on the verbal (semantic sorting) and visuospatial (non-verbal sorting) storage the RD children performed close to their peers only up to 3 digits load, and struggled with more digit strings.

The working memory difficulties with a reduced digit span, is known from the DMD group as well, showing difficulties with forward and backward digit span (Billard et.al.1998, Wingeier et.al.2011). Hinton et.al. (2004) has investigated this deficit in short-term memory further and found a specific limitation in “immediate verbal span” showing as equally diminished both forward and backward digit recall, suggesting deficits in span length rather than manipulation capacity. Other studies have confirmed this and suggested that impaired memory for sequence could be an underlying mechanism for the observed working memory deficit.

How does a DMD reader struggle? One example is a boy not able to read at age 16. With general abilities within normal (around mean IQ in the DMD group), he had early grasped the concept of letters. He could recognize all the letters in any word, but he was not able to put them together to a meaningful word. He could name each letter rapidly in sequence, but wasn't able to “see” or “hear” any words as a result. There was no connection between the letters, indicating a single processing of each letter without the crucial link to a context or a bigger picture. Contrary to most dyslexic children, his rapid naming skills are intact and not particularly “sluggish”. In parallel his digit span memory was poor, indicating that the rapid naming didn't “stick” long enough to comprehend a full word. In addition he could be confused by the sequence in which he remembered the letter items, making words non-recognizable. In parallel there is a possibility that the phonological inner processing, listening to his own rehearsal and uttering of the letters had no meaning to him, indicating a phonological loop deficit. In this boy these difficulties prevented him from breaking the code of reading, whereas in others these difficulties can affect efficient reading, reading speed and comprehension. His mother had trained with him for many years, but had lost motivation when he didn't make any progress despite daily reading sessions. “It was like he had forgotten the smart things he learnt yesterday, and sleeping on it didn't make it stick”, she said.

Struggling with the analytic mode of reading, this boy showed no global mode skills as he didn't recognize any other words than his own name – with a little help from the first letters. He also showed a persavativeness in analyzing problems, showing lack of cognitive flexibility when working with the Wisconsin Card Sorting Test (WCST). In WCST the same solution is applicable in a number of series, and then a new sorting routine is required. In spite of comprehensive clues and assistance he wasn't able to let go of the first method he came up with and didn't come up with any right solutions, indicating that attentional shifts of reading modes also would be difficult for him.

Narrative abilities are connected to this global state of reading and listening, shown to be inferior and impaired in a DMD group compared to a group of typically developing children (Marini et.al.2007). Narratives are a highly executive memory process, holding on to the storyline, sequencing events and points throughout the story.

Longitudinal studies of children with early language impairments indicate that the language problems will become more specific and less severe during the pre-school years. This is consistent with the findings from studies of children with DMD, where the language deficits seem to become less profound over time and more specifically connected to verbal memory, expressive language and attention. Receptive language and visuo-spatial abilities are spared in most DMD children. (Cyrulnik et.at. 2008). This supports the idea of development from the general to the specific.

The DMD poor readers share several characteristics with most descriptions of dyslexia, especially with the underlying verbal working memory deficit, sequencing deficits and difficulties with divided and shifting attentional focus. These core deficits as well as missing or insufficient overt or internal speech and insufficient pre-articulatory verbal code in reading suggest a cerebellar dysfunction (Ackerman 2008). In addition the ideas of dysfunctional visual attention shifts (Bosse et.al. 2007), phonological defects and underlying deficits in implicit (Folia et.al. 2008) and procedural learning suggest a basic cerebellar role in dyslexia, and thus in DMD poor readers.

The cerebellar hypothesis of dyslexia

Even though the relationship between reading abilities and cerebellar function is unclear, neuroimaging in cerebellar lesion patients are showing cerebellar abnormalities in children and adults with dyslexia (Eckert et.al. 2003, Vlachos et.al. 2007). Assessments of

reading and phonological skills in these groups reveal major difficulties in cognitive areas associated with the cerebellum (Ben-Yehudah & Fiez 2008). Even though the dyslexia group consists of several subgroups, common gross motor clumsiness seen in children with developmental dyslexia are striking, also suggesting a common cerebellar motor role (Moe-Nilssen et.al. 2003). A subgroup of children struggling with reading and writing is referred to as Developmental Coordination Disorder (Alloway 2006), presenting with motor clumsiness and motor developmental delay in addition to the working memory deficits. Even though cerebellar function is highly connected to motor control, including eye motor control, balance and postural stability (Stoodley et.al. 2011), we here focus on the cognitive function related to reading, considering the obvious motor disabilities in the DMD group. The motor factors in cognition deserve further investigation, suggesting that motor function and cognitive ability is closely connected.

Nicholson et.al. (2001, 2010) suggests the cerebellum may have a special role in reading acquisition, considering its role in procedural and implicit learning. In addition the importance of inner speech to reading, simulating the utterance of a word both to verbal working memory and to the building of meaning comprehension, the cerebellum is emerging as important to fluent reading. Children with cerebellar lesions are less able to detect mismatch between orthographic and phonological information when reading, failing to correct errors in a learning process as well. They also process and remember familiar words more effectively than non-words and novel words, suggesting a learning deficit confronted with new material (Ben-Yehudah & Fiez 2008). Compared to the DMD group, these children will have had a normal cerebellar development and language experience that comes before the lesion, while the DMD children probably are developing with a defect in procedural learning mechanisms. Hence the “non-stick”-experience in a consolidation phase of learning.

The cerebellum is involved in a variety of linguistic functions as well as processing capacity needed for fluent reading, evident from studies of cerebellar lesion patients and fMRI studies of controls carrying out language based tasks. Cerebellar language processing is apparent from studies of patients with cerebellar degeneration and ataxia, showing significantly poorer performance in verbal fluency (both phonetic and semantic) and word stem completion tasks than controls (Stoodley & Schmamann 2009), as well as deficits in attention and memory. A group of children (N=19) with cerebellar lesions showed a specific pattern of visuospatial, language sequencing and memory problems (Levisohn et.al. 2000).

Cerebellar activation is manifested during reading (Cyrulnik 2008), and is also important in linguistic production (Silveri & Miscigna 2000, Leggio et.al. 2008 & 2011, Molinari et.al. 2008), verbal fluency (Stoodley et.al. 2011), linguistic perception and phonological grouping (Leggio et.al. 2000 & 2011). Specifically the cerebellum is responsible for the temporal organization of a pre-articulatory representation of verbal utterance and sequencing of syllables during overt speech production (Ackerman 2008). That is the ability to rehearse, prepare and put together verbal information in an “auditory image” or form of “inner speech”, most relevant when reading silently (Ackerman et.al. 2004, Ackerman 2008), or processing of auditory information. Mutism and agrammism are associated with cerebellar damage, and Eckert et.al. (2003) even suggested cerebellar dysfunction might be a cause of developmental dyslexia.

The cerebellar hypothesis of dyslexia includes behavior symptoms in connection to reading, characterized as difficulties in skill automatization, and connects reading difficulties to neurobiological markers in the cerebellum. Patterns of cognitive information processing and motor skills are predicted by cerebellar dysfunction, and dyslexics are showing impaired implicit learning according to cerebellar abnormality (Nicolson et.al. 2001).

The different hypotheses of dyslexia are presenting explanations on various levels, i.e. structural, cognitive and neural levels. Considering the wide heterogeneity of the dyslexia group, there is no surprise that each hypothesis alone do not account for all variations (Stoodley & Stein 2011). The DMD reader is characterized within most hypotheses, struggling with some phonological, verbal working memory, sequencing, and attentional issues, opening the question if the DMD reader group is just as multifaceted as the dyslexic group, or do most DMD readers share all the characteristics?

The cerebellar structures underlying language processing is located mostly in the right hemisphere and partly in the vermis (Fabbro et.al. 2000, Schweizer et.al. 2010, Stoodley & Stein 2011). Neuroanatomical findings in dyslexic adolescents and adults support this hypothesis (Mariën et.al. 2009), concluding that the right cerebellar size correlated significantly with measures of reading, spelling and language related to dyslexia (Eckert et.al. 2003).

Language deficits following right cerebellar lesions are described as being due to the impairment of verbal working memory involved in language processing, and other aspects of

language production such as verbal fluency. The deficits observed controls the temporal and sequential organization of the neurofunctional systems involved in the production of words and sentences rather than impairment of specific modules of the language system (Silveri et.al. 2000, Leggio et.al. 2000, 2008, 2011). The sequence detection of letters determines the understanding of words, and the sequence of words will have a great impact on comprehension of meaning of text. The same will apply to spoken syllables, words and meaning. This will be in parallel to the episodic buffer in the theoretical model of working memory (Baddley et.al. 2011) where sensory input results are kept for executive manipulation – for example problem solving using certain known rules or methods.

The cerebellum is a central part of skilled motor and mental performance, but even midbrain structures contribute to procedural flow. Disruption of automatic speech following a right basal ganglia lesion suggests that the basal ganglia have a role in linguistic automation in general (Liebermann 2000). Reading acquires automatic control of both motor and cognitive skills, in attention shifts, and handling information on different level from details to getting the whole picture. Both prefrontal areas, basal ganglia and the cerebellum are activated during reading, illustrating the central role of the fronto-cerebellar pathway. This will imply that a variety of disturbances along this path is associated with reading difficulties.

There is a long list of potential cerebellar deficits that will be relevant for both the working memory problems and difficulties with reading found in many DMD boys. Illustrated by Baddeley's model of working memory, both sensory specialized and modality general items of the model will be relevant for understanding the DMD working memory problems. Placing the working memory function foundation in the cerebellum and the fronto-cerebellar pathway, the disturbed cerebellar structure and dysfunction of DMD cerebellum will add up as a viable explanation for observed cognitive deficits. According to the cerebellar hypothesis of dyslexia, handling verbal information acquired in a phonological loop, rehearsing and consolidating memory with time, will put load on the cerebellar and associated circuits. In DMD where storage capacity is limited, followed by incorrectly or delayed sequencing the information, the phonological – and other verbal handling processes are compromised. Children able to compensate with shorter processing time can overcome this limit by doing more iterations faster, and thereby maintain a reading capacity. DMD compensating strategies are not included in any of the research material listed in references, and the reading tests are standardized in normal populations. The learning capacity of DMD

children is reported to be as well as their peers (Hinton 2006), but they will need more time to process the given information and extract relevant details from it – whereas orally or written. There might even be an extra difficulty for them to remember the sequence of given information, adding to the rehearsal load. Sequencing, binding and verbal memory deficits are candidates for adding to difficulties in metacognitive skills (Donders & Taneja 2009), social understanding, level of knowledge and general academic functioning.

CONCLUSION

Can the reading difficulties in DMD be explained by sequencing deficits in verbal working memory as a consequence of dystrophin deficiency in cerebellar purkinje cells? Defined within the dyslexic group, there is no doubt that a large subgroup in DMD has limited reading skills. Difficulties on procedural, attentional and phonological level adds to the risk of dyslexia in DMD. Visual attention deficits, reduced verbal memory span, and verbal fluency as well as inert cognitive flexibility, is highly present within the DMD group and known to hamper fluent reading on different levels. The cerebellar contribution to these deficits are well documented within dyslexia research, suggesting overlapping symptom profiles with several groups of neurodevelopmental disorders as well (Alloway 2006). Sequencing deficits in verbal working memory is identified as a major obstacle to fluent reading, both well documented in DMD subgroups and in cerebellar lesion groups. Disturbed sequencing of perceived information could be an important underlying factor, especially in understanding short digit memory span, but is not a sole explanation of the reading difficulties observed. Other working memory factors and executive functions are abundantly present in the DMD group as well, including the binding ability – thought to affect both short time memory span, cognitive flexibility, attention shifting and context associations in reading. This needs further exploration, subdividing the DMD group into functionally comparable objects and populations when it comes to genetical profile and age.

Cerebellar contribution to cognitive function is recognized and specific working memory function seems to be heavily supported by cerebellar regulation. Concluding with the specific cognitive deficits presented in DMD being a consequence of cerebellar dysfunction alone, will be a long shot. With a diffuse modulating effect of neurodevelopment and possible compensating effects of glycoprotein complexes on cell level and a fronto-cerebellar network on a broader level, the cerebellum is only one part in combined and complex brain

processes. DMD could with these considerations be redefined as a neurodevelopmental disorder with a broad spectrum of cognitive sequelae depending on genetic patterns and modulating factors following brain development. Some – but probably not all DMD patients will present with gene mutations causing tissue specific cerebellar dystrophin deficiency. There is no doubt from research evidence that this could be an explanation for certain cognitive deficits in DMD, sharing some of the characteristic cognitive deficits with cerebellar lesion patients and some similarities with typical cerebellar syndromes and developmental cerebellar deficits – including dyslexia.

Still there are several problems with interpretations of the different findings, with a wide variability in the DMD groups studied. Further there are clearly other parts of the brain than the cerebellum being affected by lack of dystrophin, and studies of dystrophin deficiency are largely performed post mortem, by biopsy of muscle tissue or on animal models. Affected cognitive areas include executive functions, working memory and reading disabilities, recruiting the frontal-striate-cerebellar network equally. Dystrophin deficiency is actualized in the hippocampus, amygdala and neocortex as well as cerebellum, also presumed to affect general mental abilities and working memory specifically.

Full length dystrophin is at large risk for mutations, including the Dp427-P variants important for prenatal cell migration and development in the cerebellum. Will it be possible to imagine mutations only affecting dystrophin isoforms present in cerebral tissue without cerebellar dysfunction? Considering the close relationship through cortico-cerebellar pathways, it will be difficult to isolate the two, regarding the symbiosis to be a possible compensating factor in potentially dysfunctional obstacles along the path.

An important question will be if all cognitive declines associated with DMD have their origin in the cerebellum. Isoforms present in cerebral tissues may strongly contribute to neural activation of the fronto-cerebellar pathway. Particularly dystrophin expressed in the hippocampal granule cells will contribute to memory dysfunction. As a consequence, the cerebellar dysfunction in DMD may be responsible for the sequencing deficits and the explanation for more general executive and memory related difficulties may include the fronto-cerebellar neural pathway.

There are still many questions to be asked and answered about DMD. Why do we see a delayed, but not totally dysfunctional development of muscle and brain tissue? How do

these tissues work at all without dystrophin? - Answers lay probably partly in the dystrophin glycoprotein complex rather than the dystrophin itself. Mutations affecting the complex binding site clearly have more devastating effects on the complex bindings than mutations elsewhere. Genetic mutations affecting the associated members of the glycoprotein complex also present cognitive deficits, suggesting that the genetic interaction with this complex should be considered in the DMD cognitive profile.

Thinking of the large variety of genetic mutations associated with DMD, at present registered more than 25000 different mutations and combinations in the Leiden Muscular Dystrophy database, there is not so much a question of correlating size and location of gene mutations, but more a question of how the combination of mutations will influence brain and muscles depending on the dystrophin isoforms present at different developmental stages. Mutations in some locations have more devastating effect on cognitive functioning than others, and likewise can a person with several point mutations in less affecting places can have minor dysfunction compared to a person with one small point mutation in one risky location. How do we even sort out the difference between multifaceted specific, but core cognitive deficits and a global mental retardment – if there is one?

How the deficiency of fetal tissue dystrophin isoforms interacts with developmental processes is still in the dark. Drawing parallels with premature babies have clearly process faults considering most preterm babies have intact dystrophin levels during last weeks of gestation. Still DMD and preterm babies share some sequelae in anatomical structure and cognitive areas indicating both groups have generalized cerebellar deficits. The results are increased cerebellar and cerebral volume, reduced neuronal activity and different degrees of dysfunction, as similarly observed in other neurodevelopmental disorders. Probably will the developmental processes will both be disturbed by and in some way compensate for the missing dystrophin. And there will be cases when the DMD gene expression is too destructive to be consistent with life, which in most cases will go by unnoticed. Further research is needed to shed light upon the developmental effects of a dysfunctional cerebellum in a growing brain.

An understanding of the cerebellar network as crucial to cognitive and affective functioning as well as motor functioning is established. The cerebellum is no lesser brain, and cerebellar lesions implement huge negative impact on smooth cognitive function, especially if the development process is compromised. This perspective will broaden the view on several

different areas of psychiatric disorders in children, as schizophrenia, autism spectrum and attention disorders (ADHD/ADD). It is important not to underestimate the effect of acquired and congenital lesions to the cerebellum in children, and look into the possibility that different diagnoses have overlapping dysfunctional cerebellar circuits. The role of the cerebellum in a variety of processes supporting efficient reading is indisputable, but the definition of dyslexia is wider than ever before, disputing the idea of one single explanation being sufficient.

There are several considerations to be made regarding construct validity of both reading and working memory concepts, and the wide span of research focuses in this multi-disciplinary approach. Tissue analyses from animal models parallels neuropsychological tests of cerebellar lesion patients, adding exponentially to the amount of sources of errors. Lesion studies are difficult to standardize due to different sources of injury and highly unpredictable outcomes on a neuronal level. There are currently no methods of measurement of brain dystrophin in living humans, and genetic mapping is emerging, but gives no faultless method of sectioning subgroups of DMD. The whole idea of diagnosis categories might stand for a fall, laying the ground for investigating specific cognitive difficulties as result of complex developmental and functional factors.

Comparing the reading ability of patients with cerebellar lesions to DMD patients have other considerations as well. Acquired dyslexia is a result from a neural damage to a fully developed system. Developmental dyslexia on the other hand is a disorder that prevents the developing reading system from becoming efficient and automatized. Considering about half of the DMD group has moderate or severe reading difficulties, there is still the other half characterized as “normal” readers. Classifying children within a group having “normal” reading skills does not rule out possible individual difficulties in reading acquisition, effecting the reading process or slowing down the reading speed. Considering the amount of underlying reasons for reading difficulties and the numerous hypothesis of dyslexia, the cerebellar dysfunction in DMD might not be the only potential explanation for the observed difficulties. This deserves further investigation, suggesting that the cerebellar dystrophin deficiency is present in most DMD children possibly affecting sequencing and verbal working memory more or less, but that there are other executive and memory deficits presenting as a consequence of lack of dystrophin that could be a part of the explanation as well.

The deficits in verbal working memory and sequencing especially have wide impacts on academic functioning. Firstly the ability to read and to comprehend written material is

compromised. Secondly there is a link between verbal working memory and the ability to learn a second language at all ages, i.e. the ability to learn sound patterns in new words. (Alloway 2006). Thirdly sequencing difficulties and generally compromised working memory affect the ability to build a narrative, hold on to a story line and keep track of a simple how-to-do-list in everyday tasks. When sequences of social behavior are difficult, general social communication and interaction is compromised.

Research on intervention strategies addressing the specific cognitive deficits and especially reading challenges needed in the DMD group is sparse. Further work will be needed to establish test procedures and intervention programs to ensure the best outcome for boys in this group. Screening is probably required at the age of 4 (Kjærgård et.al. 2006), proceeding shortly after diagnosis, in order to discover the children at risk for reading difficulties. In addition some DMD children are at risk for pervasive disorders, which should be addressed with the proper understanding of underlying factors corresponding to the DMD genetics.

The more cumulated mutations in vulnerable areas the larger risk for cognitive and muscle dysfunction – and risk is probably the most important view when dealing with DMD children. All DMD children are at risk for learning difficulties, even though a majority is compensating well. By implementing learning strategies based less on verbal working memory skills, memorizing core knowledge and focusing on non-verbal methods, the DMD children can better compensate and put less strain on mental capacity. Not mentioned in any DMD research found in this work is the reduced level of energy these boys experience both physically and mentally. Training and daily demands will have to be on a level for them to cope with, balancing the need of stimulation and rest. Efficiency will be an important focus in order to prevent mental exhaustion. In a daily pedagogic setting it will be necessary to prioritize the most important issues to address. In daily life "the remediation for such an impairment may be relatively straightforward: speaking more simply, using shorter sentences, repeating information, and presenting information with contextual cues or visual stimuli may all be means of enhancing the learning and life of a child with DMD." (Hinton 2000).

With a heavy focus upon general ability testing as a measure of cognitive function in the DMD group, there is a chance of missing underlying difficulties and opportunities to compensate and stimulate. It will be of crucial importance for the boys (and carrier girls) to have a neuropsychological assessment of language, sequential and working memory deficits

early in development. In a psychological perspective assessment of risk and vulnerability issues will be important in order to meet the child's specific need of language, academic, and emotional support at an early stage. Especially when the cognitive deficits can be subtle or even overshadowed by motor dysfunction, will it be crucial to specify pedagogic challenges and possible difficulties to provide adequate support. To develop coping skills, independence and feeling of agency, it will be important for the child to avoid misunderstandings from supporting adults concerning own capacity and abilities. There is also a question of fatigue affecting cognitive function as well as motor performance.

Reading is fundamental for participation in public life and having access to written information and knowledge is considered a human right. Children at risk for reading failure have a right to be identified and supported, whether they are dyslexic or not. A significant DMD subgroup will experience reading difficulties preventing them from common knowledge sources. Acknowledging the reading limitations early on, working with non-literate ways of learning is compulsory in other groups struggling with sensory deficits like hearing or sight. Working memory deficits could be a parallel reason for scaffolding basic reading and learning skills early on.

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